AMENDMENTS

IN THE SPECIFICATION

Abstract

The present invention highlights the role of acetyl-CoA carboxylase through its product malonyl-CoA in regulating fatty acid oxidation and synthesis, glucose metabolism and energy homeostasis. It discloses transgenic mice with inactivating mutations in the endogenous gene for the acetyl-CoA carboxylase 2 isoform of acetyl-CoA carboxylase. Inactivation of acetyl-CoA carboxylase 2 results in mice exhibiting a phenotype of reduced malonyl-CoA levels in skeletal muscle and heart, unrestricted fat oxidation, and reduced fat accumulation in the liver and fat storage cells. As a result, the mice consume more food but accumulate less fat and remain leaner than wild-type mice fed the same diet. ~~These results demonstrate that inhibition of ACC2 acetyl-CoA carboxylase could be used to regulate fat oxidation and accumulation for purposes of weight control.~~ The instant invention provides a useful animal model to regulate malonyl-CoA production by ACC2 in the

regulation of fatty acid oxidation by muscle, heart, liver and other tissues. They also identify potential inhibitors for studying the mechanisms of fat metabolism and weight control.

IN THE CLAIMS

Claims 1-14 (canceled)

Claim 15 (currently amended): A method of screening for an inhibitor of acetyl-CoA carboxylase 2 isoform activity, comprising the steps of:

administering a potential inhibitor to one or more wild type mouse; and

screening said one or more mouse for a phenotype exhibited by a transgenic mouse~~, said phenotype comprising:~~ whose genome comprises a homozygous disruption of an endogenous ACC2 gene for the acetyl-CoA carboxylase 2 isoform of acetyl-CoA carboxylase, wherein said disruption inactivates said gene and wherein said mouse does not produce any functional acetyl-CoA carboxylase 2.

~~a metabolic reduction in malonyl-CoA production in skeletal muscle and heart;~~

~~unrestricted fat oxidation and reduced fat accumulation in the liver and fat storage cells;, and~~

~~consuming more calories than said one or more wild-type mouse;~~

selecting the inhibitor when given to a wild type mouse whose phenotype is exhibited the same as that of the transgenic mouse.

Claims 16-23 (canceled)

Claim 24 (currently amended): The method of claim 15, wherein said phenotype comprises; ~~transgenic mouse has a mutation in an endogenous ACC2 gene for the acetyl-CoA carboxylase 2 isoform of acetyl-CoA carboxylase, said mutation inactivating said gene thereby resulting in a lack of expression of a functional acetyl-CoA carboxylase 2 isoform.~~

a metabolic reduction in malonyl-CoA production in skeletal muscle and heart;

unrestricted fat oxidation and reduced fat accumulation in the liver and fat storage cells; and

consuming more calories yet accumulating less fat than said one or more wild type mouse;

Claim 25 (currently amended): The method of claim ~~24~~ 15, wherein one or more exons of said ACC2 gene has been deleted.

Claim 26 (original): The method of claim 25, wherein said exon(s) have been replaced with heterologous DNA sequences.

Claim 27 (currently amended): The method of claim 26, wherein said heterologous DNA sequences comprise ~~an~~ a hypoxanthine phosphorylribosyltransferase expression cassette.

Claim 28 (currently amended): The method of claim 27, wherein an exon encoding a biotin binding motif of ACC2 is replaced with ~~an~~ a hypoxanthine phosphorylribosyltransferase expression cassette.

REMARKS

Status of the Claims

Claims 15 and 24-28 are pending. Claims 1-14 and 16-13 have been cancelled as drawn to non-elected invention. Claims 15 and 24-28 are rejected. Claims 15, 24-25 and 27-28 are amended.

No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Objection to the specification

The Examiner states that the instant abstract appears to comprise over 150 words. Applicants have amended the abstract to a paragraph within the limit of 150 words and thereby overcoming the objection. In addition, Applicant encloses corrected drawings.

The 35 U.S.C. §112 First Paragraph Rejections

Claims 15 and 24-28 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The Examiner argued that the specification of this application, while being enabling for a transgenic mouse whose genome comprise a homozygous disruption of an endogenous ACC2 gene for the acetyl-CoA carboxylase-2 isoform of acetyl-CoA carboxylase, wherein said disruption inactivates said gene, and wherein said mouse does not produce any functional ACC2, does not reasonably provide enablement for any other transgenic mice embraced by the claims. According to the Examiner, the specification therefore does not enable any person skilled in the art to which it pertains to make and use the invention as commensurate in scope with these claims.

The instant application is directed to a method of screening for an inhibitor of acetyl-CoA carboxylase 2 isoform activity comprising administering to one or more wild type mouse and screening said one or more mouse for a phenotype exhibited by a transgenic mouse, wherein the phenotype is a metabolic reduction in malonyl-CoA production in skeletal muscle and heart, unrestricted fat oxidation and reduced fat accumulation in the liver and fat storage cells, and consuming more calories than a wild type mouse yet accumulating less fat than a wild type mouse. The

rejection is directed to the transgenic mouse embraced by the claims. Claims 15 and 24 have been amended. Amended claim 15 now includes a transgenic mouse whose genome carries a homozygous disruption in the endogenous acetyl-CoA carboxylase-2 (*ACC2*) gene. This homozygous disruption results in non-production of functional ACC2 and produces a distinct phenotype, which describes above. Importantly, the specification teaches the making and using of such a transgenic phenotype mouse with a reasonable expectation of success (pages 20-31).

Applicants respectfully submit that a person having ordinary skill in this art could readily make and use the claimed transgenic mouse, for use in screening an inhibitor of acetyl-CoA carboxylase-2. That is, a person having ordinary skill in this art could routinely prepare a transgenic mouse whose genome comprises a homozygous disruption of an endogenous *ACC2* gene for the acetyl-CoA carboxylase-2 isoform of acetyl-CoA carboxylase, so as to inactivate the gene and prevent production of functional acetyl-CoA carboxylase-2, and exhibit distinct phenotype. Accordingly, Applicants respectfully request that the rejections of

claims 15 and 24-28 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §112 Second Paragraph Rejections

Claims 15 and 24-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

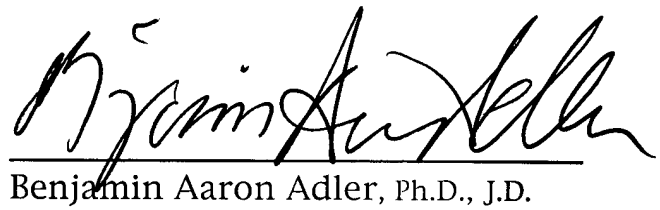
Claim 15 has been amended to add a sentence to reach the goal of the preamble in a positive process, and thereby making the claim 15 complete and definite. Rejections to claims 24-28 are moot due to the amendment to claim 15 and the fact that claims 24-28 are dependent on claim 15. Accordingly, in view of the claim amendment and argument presented herein, Applicants respectfully request that the rejections of claims 15 and 24-28 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed July 03, 2003. Applicants submit that the pending claims are now in condition for allowance. If any issues remain

outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Sept 23, 2003



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